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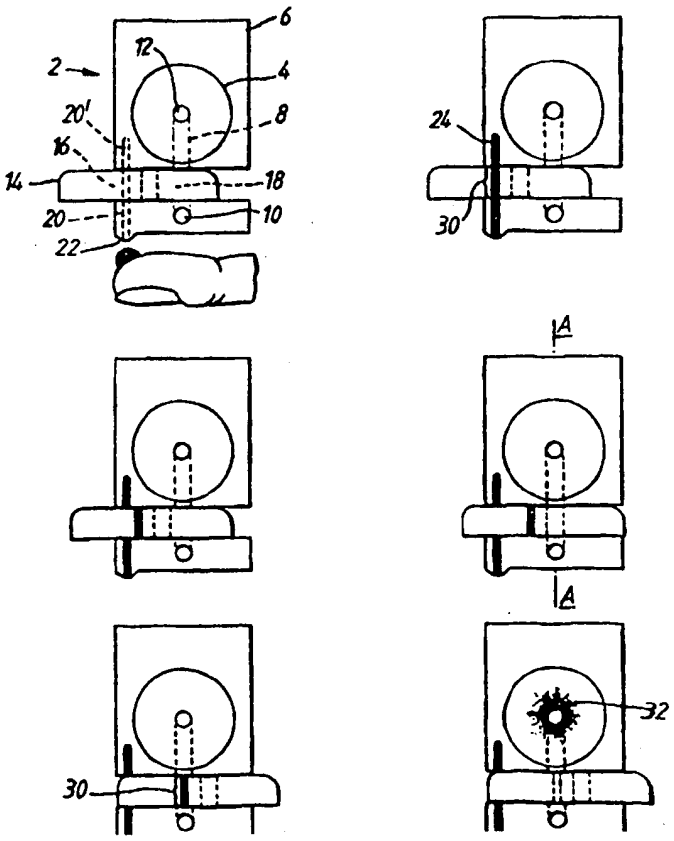
(54) Title: CHROMATOGRAPHY SYSTEM AND METHODOLOGY

(57) Abstract

A liquid chromatography system comprises a chromatographic disc (4) for resolving molecules in a liquid sample, a sample loader (2) adapted to house the disc (4), the loader (2) having one or more storage channels (16) for taking up a predetermined volume of the sample by capillary action and delivering it to the disc (4) and means (18) for delivering a buffer and/or eluent to the disc. The sample loader (2) may comprise a body portion (6) acting as a housing for the disc (4), and having (i) a loading channel (8) for conducting liquid onto or through the disc (4), comprising an afferent portion having an inlet (10) for conducting liquid to the disc (4) and an afferent portion having an outlet (12) for conducting liquid away from the disc, and (ii) a selector element (14) (e.g. a rotatable disc or a slideable bar) movably mounted on the body portion (6) so as to break the afferent portion of the loading channel (8).



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CHROMATOGRAPHY SYSTEM AND METHODOLOGY

The present invention relates to improvements in liquid chromatography apparatus and methodology, and in particular to chromatography systems for use in clinical laboratories for routine biochemical analyses.

Clinical laboratories are subject to increasing pressures to cut costs, but at the same time have to deal with an ever-increasing workload. There is therefore a need for laboratory apparatus and methodology that permits clinical data to be accumulated quickly and cost-effectively, without compromising the accuracy required for reliable determinations.

Many routine clinical procedures involve the analysis/assay of specific molecules. Examples of clinically important molecules include glycated haemoglobins, iso-transferrins (in the diagnosis and monitoring of diabetes and alcoholism, respectively) and particular drugs (for monitoring drug dosage or abuse).

Currently available procedures for the analysis/assay of such molecules include electrophoresis (followed by spectrophotometry) and liquid chromatography (particularly high performance liquid chromatography, or HPLC). However,

these techniques are slow, expensive and labour-intensive. In particular, traditional liquid chromatography suffers from many drawbacks as a quantitative routine clinical method: (1) The methods are based on the use of columns which usually contain a vast excess of packing material compared to the amount of analyte. Since column materials (especially those for use in affinity chromatography) represent a significant portion of the cost of an assay, this wastes resources. (2) Packing materials for traditional chromatography columns usually require the application of considerable pressure to move the sample into the column and to subsequently elute it during analysis. This has far-reaching consequences on the design of both the chromatography apparatus and the column itself, leading to chromatography systems with elaborate pumping and valving mechanisms which require computer control and which are expensive to buy and maintain. (3) Liquid chromatography involves the use of relatively large volumes of many different solutions and reagents, which can be conveniently stored only at room temperature under non-sterile conditions. The risk of chemical degradation and/or microbial contamination is therefore high, and the quality of the results obtained with traditional liquid chromatography therefore can become unreliable with time as a given batch of reagents deteriorates. In some cases, this problem is so acute that reagents must be prepared on a

daily basis as required, which is labour-intensive and can lead to non-uniform results.

Some attempts have been made to make column chromatography more efficient by using column material in the form of chromatographic discs or membranes (see e.g. Josic et al., (1992) Journal of Chromatography, Vol. 590, pp. 59-76). In such discs, the height of the packing material is smaller than the diameter. However, the use of chromatographic discs in conventional chromatographic applications has met with minimal success to date, and chromatographic discs are not commercially available.

The present invention provides a liquid chromatography system and methodology which is relatively inexpensive, quicker to use, not labour-intensive and which permits the use of large quantities of reagents, column buffers and column packing material to be avoided.

The invention provides a liquid chromatography system comprising: (a) a chromatographic disc for resolving molecules in a liquid sample; (b) a sample loader adapted to house the disc, the loader having one or more storage channels for taking up a predetermined volume of the sample by capillary action and delivering it to the disc; and (c) means for delivering a buffer and/or eluent to the disc.

The chromatographic disc may be self-supporting. Alternatively, its form may be maintained by the housing in the sample loader.

The chromatography system according to the invention may further comprise means for analysing an eluted sample, for example a spectrophotometric device. U.V. detectors may be usefully employed, particularly when the relative proportions of different species of molecule need to be determined quickly and easily. In some cases, however, the sample may be analysed by direct visual inspection (perhaps after mixing eluate with specific reactants), and such an approach may be particularly advantageous when testing simply for the presence or absence of a particular molecule (e.g. a drug).

Some or all of the components of the chromatography system of the invention may be suitable for disposal after use, i.e. sufficiently compact and inexpensive to be treated as laboratory consumables. When intended to be disposable, the system is advantageously closed, all buffers and reagents being included in premeasured and sealed aliquots sufficient for conditioning one or more discs or eluting one or more samples. This circumvents the customary reconstitution of and manual handling of eluents (thus avoiding contamination) and also permits long-term storage

(for example at -20 degrees centigrade or +4 degrees centigrade), obviating the need for continually making new batches of buffers and reagents and so avoiding problems arising from reagents deteriorating over time.

Eluents for use in closed systems can be manufactured to suit a range of dedicated chromatographic procedures. Moreover, different types of closed systems can be combined with different chromatographic discs (containing different packing materials), providing a common apparatus adapted for different assays (thus simplifying operator training procedures).

In a preferred embodiment of the invention, the sample loader for use in the system of the invention comprises a body portion having: (a) a housing for the disc; (b) a loading channel for conducting liquid onto or through the disc, comprising an afferent portion having an inlet for conducting liquid to the disc and an efferent portion having an outlet for conducting liquid away from the disc; and (c) a selector element (e.g. a rotatable disc or a slideable bar) movably mounted on the body portion so as to break the afferent portion of the loading channel, the selector element having at least one interconnect channel comprising the storage channel and being movable between at least two positions; (i) a load position in which the

interconnect channel completes the broken afferent portion of the loading channel such that, in use, the contents of the storage channel are in fluid communication with the disc and may be loaded therefrom onto the disc, and (ii) a collect position in which the interconnect channel is not in fluid communication with the disc, the storage channel being thereby isolated therefrom.

In a preferred embodiment, the selector element has at least first and second interconnect channels, the first comprising the storage channel. In this embodiment the selector element is movable between at least two positions; (i) a load position in which the first interconnect channel completes the broken afferent portion of the loading channel such that, in use, the contents of the storage channel are in fluid communication with the disc and may be loaded therefrom onto the disc, and (ii) an elute/conditioning position in which the second interconnect channel completes the broken afferent portion of the loading channel.

Particularly preferred is an embodiment where the selector element is movable to a storage position in which neither the first nor the second interconnect channel completes the broken afferent portion of the loading channel, such that the storage channel is isolated and the loading channel is

blocked by the selector element. This permits the sample loader and disc to be stored and/or manipulated prior to analysis without losing or contaminating the sample.

The sample loader preferably further comprises means for collecting the sample by capillary action. The collecting means may advantageously comprise a capillary collecting channel in the body portion of the sample loader, the selector element being movable to a collect position in which the first interconnect channel is in fluid communication with the capillary collecting channel such that, in use, a fluid sample can be drawn into the storage channel of the first interconnect channel via the collecting channel by capillary action.

The means for delivering a buffer and/or eluent to the disc may comprise two or more syringes feeding a common outlet, the syringes having differentially advanceable pistons such that, in use, the syringes can deliver a predetermined salt gradient. The pistons may be differentially advanced by suitable drive means, such as differentially geared or pitched screw thread drives, or differently profiled cams.

Alternatively, the means for delivering a buffer and/or eluent to the disc may comprise a flexible bag (e.g. a plastic bag) partitioned into compartments, each

compartment feeding a common outlet located at one end of the bag (the other end of the bag being closed). This embodiment may preferably further comprise means (e.g. a roller or rollers, bar or plate) adapted to progressively squeeze the bag from the closed end to the outlet end to eject the contents of the compartments at different rates such that a predetermined salt gradient is delivered. The squeezing means may be adapted to squeeze along a linear or nonlinear front, and may for example comprise a stepped or curved rod or bar.

Conveniently, at least two of the compartments of the flexible bag may be of different shape such that, in use, the ejection of the bag contents by progressive squeezing of the bag from the closed end to the outlet end produces differential ejection rates of the contents of the compartments such that the bag can deliver a predetermined salt gradient.

The squeeezing means may constitute an ancillary component of the chromatography system with which the bag device is adapted to operate.

At least one of the compartments of the bag may be shaped such that the progressive squeezing of the bag produces a constant ejection rate of the contents of the compartment.

This is useful where it is desired to provide a constant concentration of a reagent to the eluent, for e.g. reaction with one or more eluted analytes in the sample or for the stabilization of the resolved fractions of the sample.

The above-exemplified buffer/eluent delivery means are preferably adapted to deliver eluent/buffer at relatively low pressures, typically below 100 psi (for example below 50 psi, and usually below 25 psi). This exploits the fact that only relatively low pressures are required to load and elute samples on chromatographic discs (in contrast to e.g. HPLC columns), and obviates the need for expensive pumping and valve equipment: the devices described above are particularly inexpensive to manufacture and are easy to use by relatively untrained staff.

The invention also comprehends the sample loaders, chromatographic discs and buffer/eluent delivery means of the invention per se, which it is envisioned may be conveniently provided as separate system components. When provided separately, the sample loader may be adapted to house a midget column (rather than a chromatographic disc) of the type described in Ersser et al. (1986) Biomedical Chromatography, Vol. 1 (No. 4), pp. 183-188.

The invention also comprehends a method of resolving

molecules in biological fluid samples (e.g. blood samples) comprising the steps of: (a) providing a sample loader housing a chromatographic disc and having one or more storage channels each of which are adapted to take up a predetermined volume of a sample by capillary action; (b) drawing a sample into one of the storage channels by capillary action; (c) bringing the storage channel into fluid communication with the chromatographic disc; (d) loading the sample onto the disc, and (e) eluting the sample from the disc to resolve the molecules in the sample.

The invention will now be described in greater detail by way of examples of specific embodiments. The embodiments presented are by way of exemplification, and are in no way intended to limit the scope of the invention. Embodiments will be described with reference to the accompanying drawings in which:

Fig. 1 A-F is a schematic plan view of the sample loader of the invention, shown with a chromatographic disc installed and in various stages of operation.

Fig. 2 is a section through A-A of Fig. 1D.

Fig. 3 A-C are plan views of devices in the form of a bag

for delivering a buffer and/or eluent to a chromatographic disc.

Fig. 4 is a schematic front sectional view of a device in the form of an array of syringes for delivering a buffer and/or eluent to a chromatographic disc. Fig. 4B is the device in sectional side view.

With reference to Fig. 1 A-F, the sample loader 2 of the invention (with a chromatographic disc 4 loaded therein) is shown in six stages (A-F) of operation.

The loader consists of a plastic cartridge 6 acting as a housing for the disc 4. The cartridge is provided with a loading channel 8, having an inlet 10 and an outlet 12. The afferent portion of the loading channel 8 is broken by a selector element 14 in the form of a slideable bar. The selector element 14 has two channels, a first interconnect channel 16 and second interconnect channel 18, the first interconnect channel 16 comprising a storage channel. The sample loader 2 is also provided with a capillary collecting channel 20 which is broken by the selector element 14 into two portions 20 and 20'. The distal portion 20' is blind and the proximal portion 20 terminates in a nipple 22.

The steps in using the sample loader are shown in sequence in Figs. 1A-F. In Fig. 1A, the selector element 14 is shown in the collect position, in which the first interconnect channel 16 is in fluid communication with the capillary collecting channel 20, 20'. In this position, the nipple 22 can be introduced into a liquid sample (shown as a drop of blood on the tip of a finger) whereupon capillary action draws the blood sample first into the caplillary collecting channel 20, then into the first interconnect channel 16 (which now acts as a storage channel) and finally into the distal end of the capillary connecting channel 20'.

The result is a thin column of the blood sample 24 (shown in Fig. 1B), the amount of blood held in the selector element 14 representing a defined volume 30.

The selector element 14 can now be moved to a storage position, shown in Fig. 1C, in which neither the first 16 nor second 18 interconnect channels completes the broken afferent portion of the loading channel 8. The blood sample is isolated and sealed in the first interconnect channel 16, (which nows acts as a storage channel) and cannot leak away. The loading channel 8 is blocked by the selector element 14. In this position the sample can be stored (e.g. at +4 degrees centigrade) prior to further

analysis.

In Fig. 1D the sampler 2 is shown with the selector element 14 moved to an elute/conditioning position, in which the second interconnect channel 18 completes the broken afferent portion of the loading channel 8. This permits the disc 4 to be conditioned with e.g. loading buffer by pumping buffer through the loading channel 8. This step may be carried out by inserting the cartridge 6 into a dedicated instrument which mechanically moves the selector element 14 while making connection with the inlet 10 and outlet 12.

After conditioning, the sample may be loaded onto the disc 4 by moving the selector element 14 into a load position (shown in Fig. 1E). Here the first interconnect channel 16 completes the broken afferent portion of the loading channel 8 such that the contents of the storage channel (shown as the defined volume 30) are in fluid communication with the disc 4.

Loading buffer may now be pumped into the inlet 10 to drive the sample onto the disc (shown in Fig. 1F) where it spreads into the disc media (shown as 32). An elution buffer may then be pumped onto the loaded disc (optionally after returning the selector element to the

elute/conditions position shown in Fig. 1D).

Alternatively, an elution buffer (e.g. a salt gradient) can be applied immediately at the step shown in Fig. 1E, and the sample loaded and eluted in one operation.

The sample eluted after the step shown in Fig. 1F may then be passed to a detection system (e.g. a spectrophotometer), or subjected to direct visual inspection where appropriate.

The cartridge 6 of the invention may be incorporated into a multichannel system where samples are transported to different types of disc, or may form part of an off-line system where multiple samples are loaded onto a set of cartidges. Once attached to the disc medium, analytes become much more stable and this simplifies transport for later analysis (e.g. mailing would be possible, rather than sending samples packed in ice).

A system based on the sample loader of the invention may be adapted for analysing more than one sample. In this case, the distal end of the capillary collecting channel 20' is formed to run right through the cartridge 6 (i.e. it is no longer blind). Such an arrangement permits the capillary 20,20' to be washed through when in the collect position shown in Fig. 1A before a second sampling operation is conducted.

The construction of the sample loader is shown in more detail in Fig. 2, which is a section through A-A of Fig. 1D. The numbering used in Fig. 1 is adhered to as far as possible.

The cartridge 6 is of two-part construction, having an upper portion 6a and a lower portion 6b to permit access to the chromatographic disc 4 mounted in a recess 50 in the lower portion 6b which, together with the upper portion 6a, defines a disc housing 51.

The selector element 14 is positioned so as to allow fluid to flow from the inlet 10 to the disc 4, the second interconnect channel 18 acting to bridge the break in the afferent portion of the loading channel 8. The arrows indicate the direction of flow along the loading channel 8: the loading channel can be seen to continue away from the disc as an efferent portion 52.

Devices for delivering a buffer and/or an eluent to the disc are shown in Fig. 3A-B. With reference to Fig 3A, the device consists of a flexible plastic bag 122 partitioned into two separate compartments a and b by a seal 40. Each of the compartments feeds a common outlet (60). One end 80 of the bag is blind. A roller 100 is provided, which is mounted so that it can be rolled along the bag from the

blind end 80 to the outlet 60 (in the direction shown by the arrow), thus driving out the contents of the compartments a and b at different rates. As a result the combined output consists of a continually varying relative concentration of the contents of the compartments a and b, the concentration gradient reflecting the physical configuration of the seal 40.

In Fig. 3A, this is a linear seal, and so the gradient produced would be linear.

In Fig. 3B, the seal 40 is non-linear, and so the gradient produced would also be non-linear.

In Fig. 3C, the bag consists of three separate compartments a-c, compartment c being defined by a second seal 150 and of uniform shape. As a result of its uniform shape, progressive squeezing of the bag by the roller 100 produces a constant ejection rate of the contents of the compartment. The concentration of the contents of compartment c therefore remain constant with respect to the combined output of the contents of compartments a and b, and this arrangement is therefore suitable when it is desired to provide a constant concentration of a given reagent during elution, e.g. for reaction with analytes in the sample or for the stabilization of labile components of

the eluted sample.

An alternative construction for a delivery device is shown in Fig. 4. In this construction, three syringes 120 form an array feeding a common outlet 140. The syringes may have cylindrical bores, or be square in cross section. The syringe pistons 160 are driven by cams 180 mounted on a common spindle 110. Each of the cams 180 have a different profile, so that the pistons are driven at different rates. Thus, the syringes each deliver their contents at different rates so that the mix produced at the common outlet 140 constitutes a continuously varying concentration of the contents of each of the syringes. The cam arrangement is shown more clearly in Fig. 4B, where the direction of rotation of the spindle and cam and the consequent direction of piston movement are shown. The other cams (in this embodiment, each having a different profile) are shown in broken outline. The cams may be interchangeable, to permit the delivery of different gradients by switching cams.

The delivery devices can conveniently be supplied pre-packed with buffer solutions and reagents, ready for use or storage.

CLAIMS:

1. A liquid chromatography system comprising:

(a) a chromatographic disc for resolving molecules in a liquid sample;

(b) a sample loader adapted to house the disc, the loader having one or more storage channels for taking up a predetermined volume of the sample by capillary action and delivering it to the disc; and

(c) means for delivering a buffer and/or eluent to the disc.

2. A chromatography system according to claim 1 which is suitable for disposal after use.

3. A chromatography system according to claim 1 or claim 2 further comprising means for analysing an eluted sample, for example a spectrophotometric device, e.g. a U.V. detector.

4. A chromatography system according to any one of the preceding claims wherein the means for delivering the

buffer/eluent is adapted to deliver it at a pressure below 100 psi (for example below 50 psi, e.g. below 25 psi).

5. A chromatography system according to any one of the preceding claims which is a closed system, wherein the means for delivering the buffer/eluent contains a predetermined volume of buffer/eluent sufficient for conditioning one or more discs or eluting one or more samples.

6. A chromatography system according to any one of the preceding claims wherein the sample loader comprises a body portion having:

(a) a housing for the disc;

(b) a loading channel for conducting liquid onto or through the disc, comprising an afferent portion having an inlet for conducting liquid to the disc and an efferent portion having an outlet for conducting liquid away from the disc; and

(c) a selector element (e.g. a rotatable disc or a slideable bar) movably mounted on the body portion so as to break the afferent portion of the loading channel, the selector element having at least one interconnect channel

comprising the storage channel and being movable between at least two positions; (i) a load position in which the interconnect channel completes the broken afferent portion of the loading channel such that, in use, the contents of the storage channel are in fluid communication with the disc and may be loaded therefrom onto the disc, and (ii) a collect position in which the interconnect channel is not in fluid communication with the disc, the storage channel being thereby isolated therefrom.

7. The chromatography system according to claim 6 wherein the selector element has at least first and second interconnect channels, the first comprising the storage channel, wherein the selector element is movable between at least two positions; (i) a load position in which the first interconnect channel completes the broken afferent portion of the loading channel such that, in use, the contents of the storage channel are in fluid communication with the disc and may be loaded therefrom onto the disc, and (ii) an elute/conditioning position in which the second interconnect channel completes the broken afferent portion of the loading channel.

8. A chromatography system according to claim 6 or claim 7, wherein the selector element is movable to a storage position in which neither the first nor the second

interconnect channel completes the broken afferent portion of the loading channel, such that the storage channel is isolated and the loading channel is blocked by the selector element.

9. A chromatography system according to any one of the preceding claims wherein the sample loader further comprises means for collecting the sample by capillary action.

10. A chromatography system according to claim 9 as dependent on claims 6 to 8 wherein the collecting means comprises a capillary collecting channel in the body portion of the sample loader, the selector element being movable to a collect position in which the first interconnect channel is in fluid communication with the capillary collecting channel such that, in use, a fluid sample can be drawn into the storage channel of the first interconnect channel via the collecting channel by capillary action.

11. A chromatography system according to any one of the preceding claims wherein the means for delivering a buffer and/or eluent to the disc comprises two or more syringes feeding a common outlet, the syringes having differentially advanceable pistons (e.g. differentially cammed pistons)

such that, in use, the syringes can deliver a predetermined salt gradient.

12. A chromatography system according to any one of the preceding claims wherein the means for delivering a buffer and/or eluent to the disc comprises a flexible bag (e.g. a plastic bag) partitioned into compartments, each compartment feeding a common outlet located at one end of the bag (the other end of the bag being closed).

13. The chromatography system according to claim 12, wherein the means for delivering a buffer and/or eluent to the disc further comprises means (e.g. a roller, bar or plate) adapted to progressively squeeze the bag from the closed end to the outlet end to eject the contents of the compartments at different rates such that a predetermined salt gradient is delivered, the squeezing means being adapted to squeeze along a linear or nonlinear front.

14. A chromatography system according to claim 12 or claim 13 wherein at least two of the compartments of the flexible bag are of different shape such that, in use, the ejection of the bag contents by progressive squeezing of the bag from the closed end to the outlet end produces differential ejection rates of the contents of the compartments such that the bag can deliver a predetermined salt gradient.

15. A chromatography system according to any one of claims 12 to 14 wherein at least one of the compartments is shaped such that the progressive compression of the bag by the roller or bar produces a constant ejection rate of the contents of the compartment.

16. A sample loader as described in any one of claims 1 and 6 to 10, for use in the chromatography system of any one of the preceding claims.

17. Means for delivering a buffer and/or eluent as described in any one of claims 4, 5 and 11 to 15, for use in the chromatography system of any one of the preceding claims.

18. A chromatographic disc adapted for use with the sample loader of the chromatography system of any one of the preceding claims.

19. A method of resolving molecules in biological fluid samples (e.g. blood samples) comprising the steps of;

(a) providing a sample loader (e.g. the sample loader of claim 14) housing a chromatographic disc and having one or more storage channels each of which are adapted to take up a predetermined volume of a sample by capillary action,

(b) drawing a sample into one of the storage channels by capillary action,

(c) bringing the storage channel into fluid communication with the chromatographic disc,

(d) loading the sample onto the disc, and

(e) eluting the sample from the disc (e.g. by using means according to claim 17) to resolve the molecules in the sample.

20. A sample loader according to claim 16, having a disc loaded with a sample housed therein for transport via the mail.

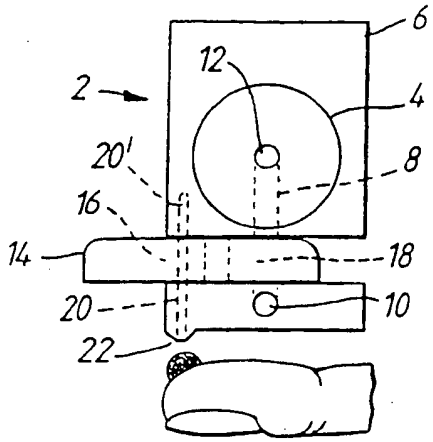

Fig.1A

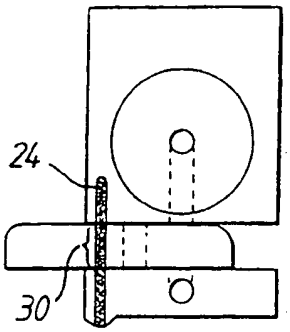

Fig.1B

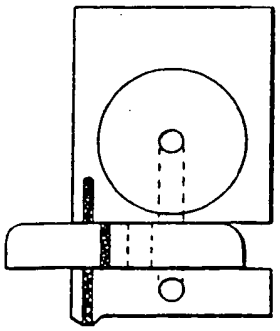

Fig.1C

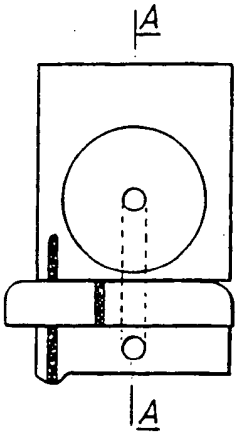

Fig.1D

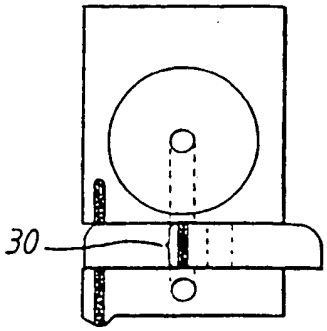

Fig.1F

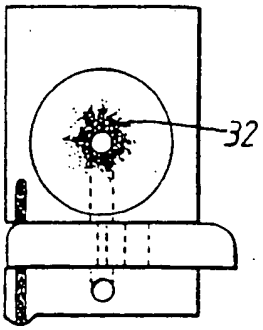

Fig.1F

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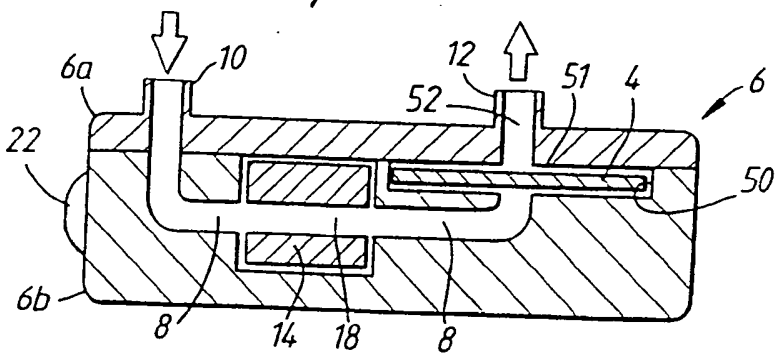

Fig.2

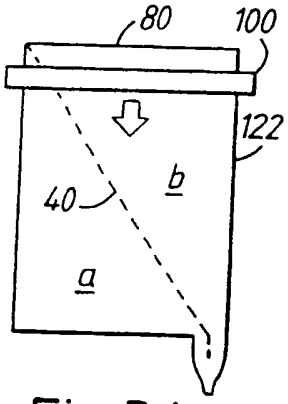

Fig.3A

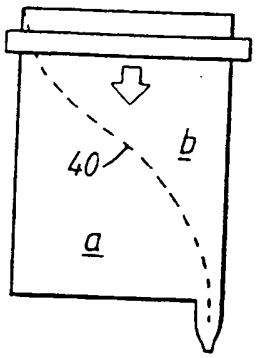

Fig.3B

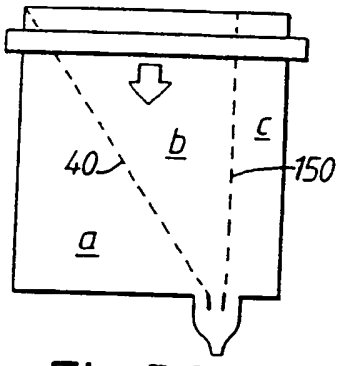

Fig.3C

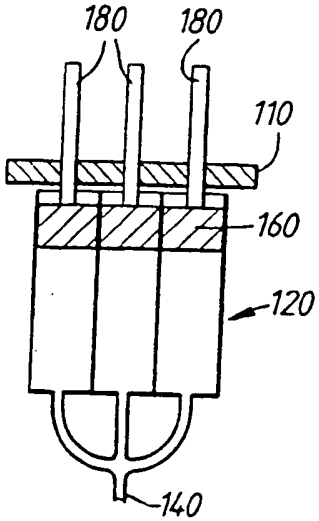

Fig.4A

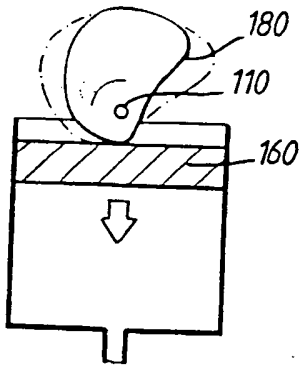

Fig.4B

INTERNATIONAL SEARCH REPORT

Inte nal Application No
PCT/GB 95/00693

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 G01N30/20

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 G01N B01L A61B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	JOURNAL OF CHROMATOGRAPHY, vol.590, 1992, AMSTERDAM NL pages 59 - 76 D. JOSIC ET AL. 'high-performance membrans chromatography of serum and plasma membrane proteins' cited in the application see page 59 - page 60, column 1, paragraph 1 see page 60, column 2, paragraph 4 - page 61, column 1, paragraph 1; figure 3 ---	1-6,9-19
Y	WO,A,93 17328 (DREW SCIENTIFIC LTD) 2 September 1993 see page 12, paragraph 1; figure 1	1-6,9-19
A	see page 3, paragraph 1 -----	8,20

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 June 1995	05.07.95

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Zinngrebe, U

INTERNATIONAL SEARCH REPORT

Inte nal Application No
PCT/GB 95/00693

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A-9317328	02-09-93	NONE	